First Principles Calculations of the pK_a Values and Tautomers of Isoguanine and Xanthine

Katherine Noyes Rogstad[§], Yun Hee Jang[†,‡], Lawrence C. Sowers[§,†], and William A. Goddard, III [†,*]

[†]Materials and Process Simulation Center, Beckman Institute (139-74)
California Institute of Technology, Pasadena, California 91125

[‡]School of Chemistry, Seoul National University, Seoul 151-747, Korea

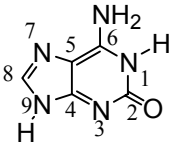
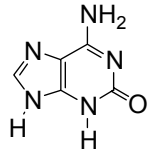
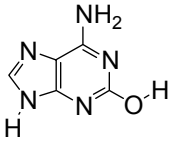
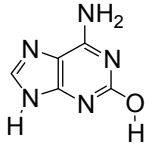
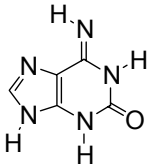
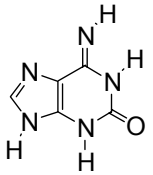
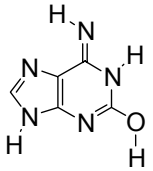
[§]Department of Biochemistry and Microbiology, Loma Linda University School of Medicine, Loma Linda, California 92350

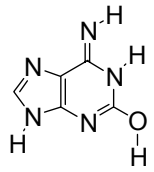
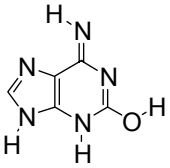
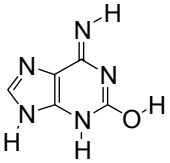
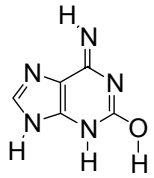
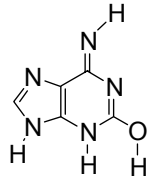
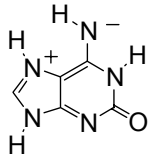
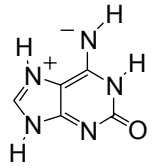
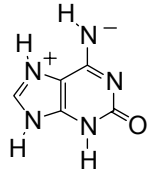
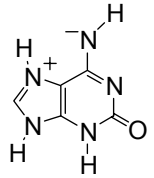
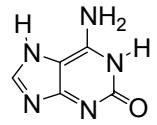
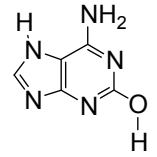
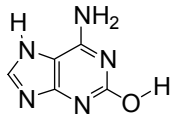
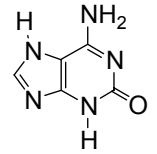
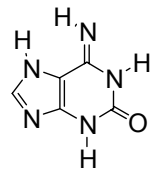
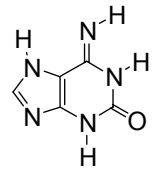
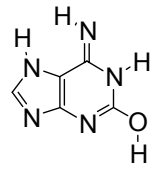
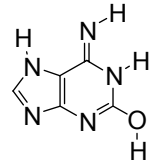
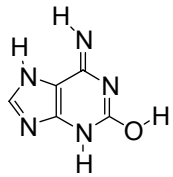
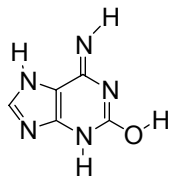
Supporting Information: Data on the tautomers and pK_a values of isoguanine and xanthine

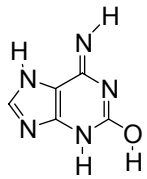
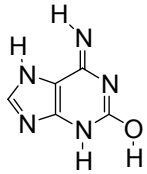
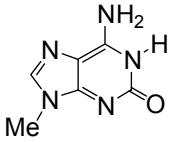
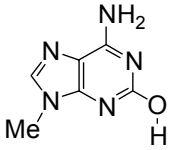
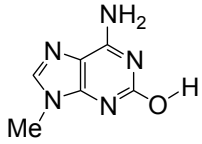
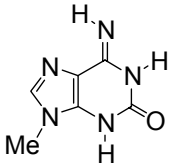
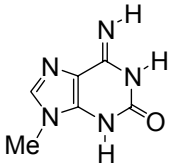
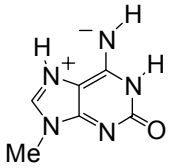
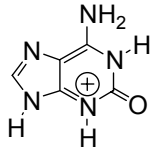
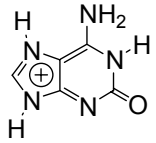
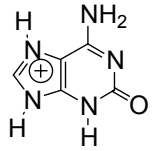
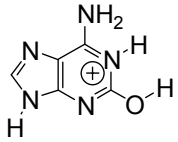
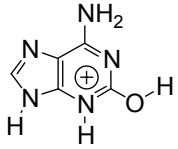
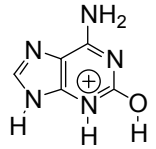
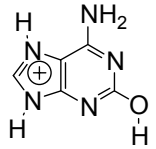
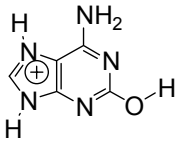
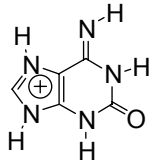
Isoguanine

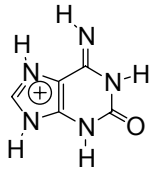
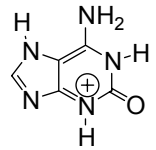
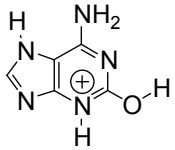
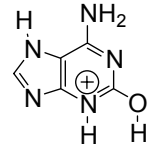
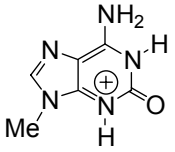
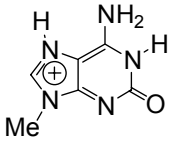
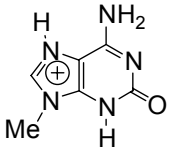
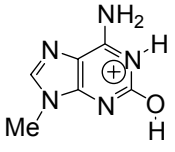
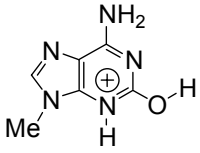
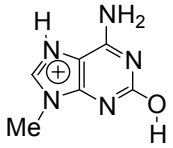
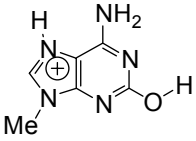
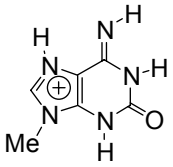
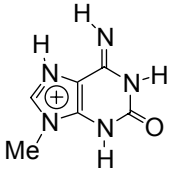
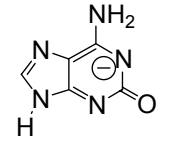
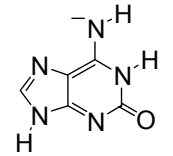
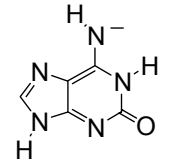
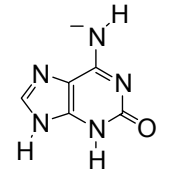
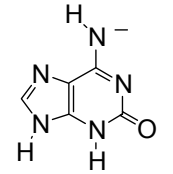
Naming convention for tautomers of isoguanine
Neutral tautomers are given a number (**1**, **2**, etc.). 9-methylisoguanine derivatives are followed by the letter "m" (**1m**, **2m**, etc.). Protonated tautomers begin with the letter "p" (**p1**, **p2**, **p1m**, **p2m**, etc.) Deprotonated tautomers begin with the letter "a" (for "anionic") (**a1**, **a2**, **a1m**, **a2m**, etc.).

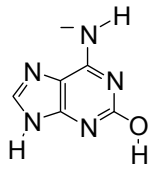
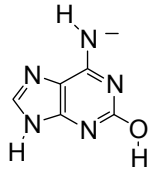
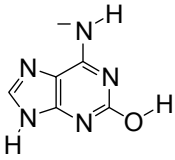
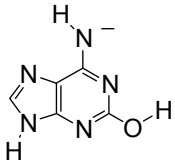
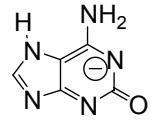
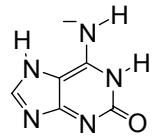
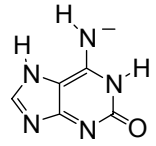
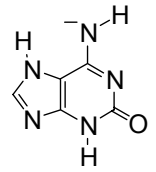
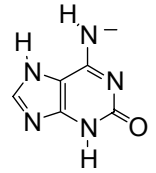
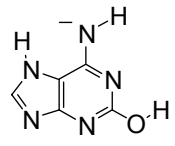
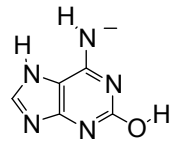
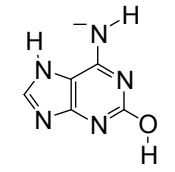
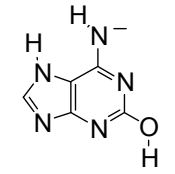
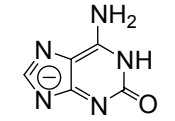
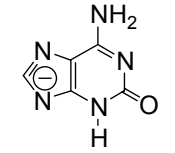
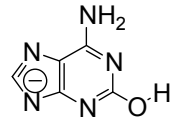
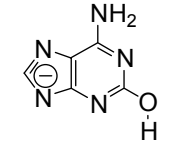
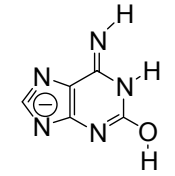
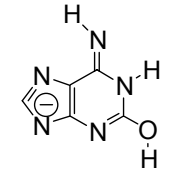
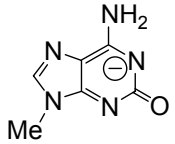
Table S1. Tautomers of isoguanine. Relative free energies ($\Delta\Delta G$ in kcal/mol) and relative populations (f) are given in relation to the most stable tautomer of a particular group. Each group is labeled in boldface. Values for both the gas phase (g) and aqueous phase (aq) are indicated for each structure.

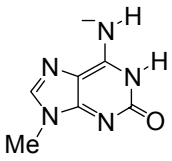
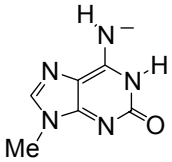
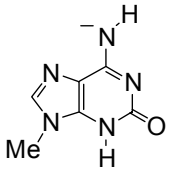
Name	Structure	$\Delta\Delta G$	f
Neutral Isoguanine			
1		^{g} 5.5 ^{aq} 0.0	^{g} 6×10^{-5} ^{aq} 0.51
2		^{g} 4.9 ^{aq} 0.2	^{g} 2×10^{-4} ^{aq} 0.38
3		^{g} 0.4 ^{aq} 6.7	^{g} 0.34 ^{aq} 6×10^{-6}
4		^{g} 0.0 ^{aq} 6.8	^{g} 0.66 ^{aq} 5×10^{-6}
5		^{g} 8.5 ^{aq} 7.7	^{g} 4×10^{-7} ^{aq} 1×10^{-6}
6		^{g} 13.7 ^{aq} 7.7	^{g} 6×10^{-11} ^{aq} 1×10^{-6}
7		^{g} 13.2 ^{aq} 17.3	^{g} 1×10^{-10} ^{aq} 1×10^{-13}

8		^{g} 19.3 ^{aq} 17.7	^{g} 4×10^{-15} ^{aq} 5×10^{-14}
9		^{g} 29.0 ^{aq} 22.5	^{g} 4×10^{-22} ^{aq} 2×10^{-17}
10		^{g} 29.0 ^{aq} 21.8	^{g} 3×10^{-22} ^{aq} 6×10^{-17}
11		^{g} 39.3 ^{aq} 24.8	^{g} 1×10^{-29} ^{aq} 3×10^{-19}
12		^{g} 38.6 ^{aq} 25.1	^{g} 3×10^{-29} ^{aq} 2×10^{-19}
13		^{g} 31.2 ^{aq} 12.2	^{g} 8×10^{-24} ^{aq} 5×10^{-10}
14		^{g} 26.3 ^{aq} 12.6	^{g} 4×10^{-20} ^{aq} 3×10^{-10}
15		^{g} 55.9 ^{aq} 17.9	^{g} 6×10^{-42} ^{aq} 4×10^{-14}
16		^{g} 43.3 ^{aq} 17.4	^{g} 1×10^{-32} ^{aq} 8×10^{-14}
17		^{g} 19.0 ^{aq} 2.3	^{g} 8×10^{-15} ^{aq} 0.010
18		^{g} 8.7 ^{aq} 8.2	^{g} 3×10^{-7} ^{aq} 5×10^{-7}
19		^{g} 9.8 ^{aq} 8.2	^{g} 4×10^{-8} ^{aq} 5×10^{-7}
20		^{g} 6.8 ^{aq} 1.0	^{g} 7×10^{-6} ^{aq} 0.10
21		^{g} 5.3 ^{aq} 7.5	^{g} 8×10^{-5} ^{aq} 2×10^{-6}
22		^{g} 3.6 ^{aq} 7.4	^{g} 1×10^{-3} ^{aq} 2×10^{-6}
23		^{g} 17.2 ^{aq} 18.3	^{g} 2×10^{-13} ^{aq} 2×10^{-14}
24		^{g} 16.9 ^{aq} 19.0	^{g} 3×10^{-13} ^{aq} 6×10^{-15}
25		^{g} 23.0 ^{aq} 22.0	^{g} 9×10^{-18} ^{aq} 4×10^{-17}
26		^{g} 16.8 ^{aq} 21.5	^{g} 3×10^{-13} ^{aq} 8×10^{-17}

27		^{g} 25.3 ^{aq} 23.0	^{g} 2×10^{-19} ^{aq} 7×10^{-18}
28		^{g} 32.3 ^{aq} 23.3	^{g} 1×10^{-24} ^{aq} 4×10^{-18}
Neutral 9-Methylisoguanine			
1m		^{g} 5.4 ^{aq} 0.0	^{g} 8×10^{-5} ^{aq} 0.56
2m		^{g} 0.7 ^{aq} 6.8	^{g} 0.24 ^{aq} 6×10^{-6}
3m		^{g} 0.0 ^{aq} 5.6	^{g} 0.76 ^{aq} 4×10^{-5}
4m		^{g} 4.9 ^{aq} 0.1	^{g} 2×10^{-4} ^{aq} 0.44
5m		^{g} 8.7 ^{aq} 8.2	^{g} 3×10^{-7} ^{aq} 5×10^{-7}
6m		^{g} 13.9 ^{aq} 8.0	^{g} 5×10^{-11} ^{aq} 7×10^{-7}
14m		^{g} 24.8 ^{aq} 11.6	^{g} 5×10^{-19} ^{aq} 2×10^{-9}
Protonated Isoguanine			
p1		^{g} 0.0 ^{aq} 0.2	^{g} 0.86 ^{aq} 0.41
p2		^{g} 17.9 ^{aq} 3.0	^{g} 6×10^{-14} ^{aq} 0.004
p3		^{g} 20.0 ^{aq} 4.1	^{g} 2×10^{-15} ^{aq} 6×10^{-4}
p4		^{g} 1.3 ^{aq} 8.8	^{g} 0.09 ^{aq} 2×10^{-7}
p5		^{g} 9.2 ^{aq} 9.6	^{g} 2×10^{-7} ^{aq} 6×10^{-8}
p6		^{g} 1.8 ^{aq} 10.3	^{g} 0.04 ^{aq} 2×10^{-8}
p7		^{g} 10.5 ^{aq} 11.9	^{g} 2×10^{-8} ^{aq} 1×10^{-9}
p8		^{g} 8.7 ^{aq} 8.5	^{g} 4×10^{-7} ^{aq} 4×10^{-7}
p9		^{g} 8.2 ^{aq} 8.5	^{g} 8×10^{-7} ^{aq} 4×10^{-7}
p10		^{g} 16.8 ^{aq} 11.2	^{g} 4×10^{-13} ^{aq} 4×10^{-9}

p11		^{g} 22.7 ^{aq} 11.5	^{g} 2×10^{-17} ^{aq} 2×10^{-9}
p12		^{g} 2.6 ^{aq} 0.0	^{g} 0.01 ^{aq} 0.59
p13		^{g} 10.7 ^{aq} 9.8	^{g} 1×10^{-8} ^{aq} 4×10^{-8}
p14		^{g} 10.0 ^{aq} 19.6	^{g} 4×10^{-8} ^{aq} 3×10^{-15}
p15		^{g} 8.1 ^{aq} 11.1	^{g} 1×10^{-6} ^{aq} 4×10^{-9}
Protonated 9-Methylisoguanine			
p1m		^{g} 0.0 ^{aq} 0.0	^{g} 0.84 ^{aq} 0.87
p2m		^{g} 15.4 ^{aq} 1.1	^{g} 4×10^{-12} ^{aq} 0.13
p3m		^{g} 19.2 ^{aq} 4.3	^{g} 7×10^{-15} ^{aq} 6×10^{-4}
p4m		^{g} 1.1 ^{aq} 6.9	^{g} 0.12 ^{aq} 7×10^{-6}
p6m		^{g} 1.9 ^{aq} 9.9	^{g} 0.03 ^{aq} 5×10^{-8}
p8m		^{g} 6.9 ^{aq} 7.1	^{g} 7×10^{-6} ^{aq} 5×10^{-6}
p9m		^{g} 5.9 ^{aq} 6.4	^{g} 4×10^{-5} ^{aq} 2×10^{-5}
p10m		^{g} 15.9 ^{aq} 11.1	^{g} 2×10^{-12} ^{aq} 7×10^{-9}
p11m		^{g} 20.8 ^{aq} 11.1	^{g} 4×10^{-16} ^{aq} 6×10^{-9}
Deprotonated Isoguanine			
a1		^{g} 15.3 ^{aq} 2.4	^{g} 6×10^{-12} ^{aq} 0.02
a2		^{g} 8.5 ^{aq} 5.2	^{g} 6×10^{-7} ^{aq} 1×10^{-4}
a3		^{g} 13.2 ^{aq} 5.9	^{g} 2×10^{-10} ^{aq} 4×10^{-5}
a4		^{g} 30.6 ^{aq} 12.4	^{g} 4×10^{-23} ^{aq} 8×10^{-10}
a5		^{g} 28.3 ^{aq} 18.9	^{g} 2×10^{-21} ^{aq} 1×10^{-14}

a6		^{g} 26.6 ^{aq} 17.8	^{g} 3×10^{-20} ^{aq} 9×10^{-14}
a7		^{g} 25.6 ^{aq} 17.0	^{g} 2×10^{-19} ^{aq} 3×10^{-13}
a8		^{g} 24.2 ^{aq} 17.8	^{g} 2×10^{-18} ^{aq} 8×10^{-14}
a9		^{g} 24.3 ^{aq} 18.2	^{g} 2×10^{-18} ^{aq} 4×10^{-14}
a10		^{g} 25.9 ^{aq} 4.1	^{g} 1×10^{-19} ^{aq} 0.001
a11		^{g} 16.6 ^{aq} 6.7	^{g} 6×10^{-13} ^{aq} 1×10^{-5}
a12		^{g} 15.2 ^{aq} 7.6	^{g} 7×10^{-12} ^{aq} 2×10^{-6}
a13		^{g} 24.8 ^{aq} 9.6	^{g} 6×10^{-19} ^{aq} 8×10^{-8}
a14		^{g} 15.7 ^{aq} 9.1	^{g} 3×10^{-12} ^{aq} 2×10^{-7}
a15		^{g} 28.1 ^{aq} 18.4	^{g} 2×10^{-21} ^{aq} 3×10^{-14}
a16		^{g} 21.2 ^{aq} 18.7	^{g} 3×10^{-16} ^{aq} 2×10^{-14}
a17		^{g} 28.7 ^{aq} 17.7	^{g} 8×10^{-22} ^{aq} 1×10^{-13}
a18		^{g} 21.3 ^{aq} 18.6	^{g} 2×10^{-16} ^{aq} 2×10^{-14}
a19		^{g} 13.5 ^{aq} 1.7	^{g} 1×10^{-10} ^{aq} 0.05
a20		^{g} 0.0 ^{aq} 0.0	^{g} 1.00 ^{aq} 0.93
a21		^{g} 9.4 ^{aq} 8.2	^{g} 1×10^{-7} ^{aq} 9×10^{-7}
a22		^{g} 8.1 ^{aq} 8.8	^{g} 1×10^{-6} ^{aq} 3×10^{-7}
a23		^{g} 27.6 ^{aq} 18.9	^{g} 5×10^{-21} ^{aq} 1×10^{-14}
a24		^{g} 19.4 ^{aq} 18.4	^{g} 6×10^{-15} ^{aq} 3×10^{-14}
Deprotonated 9-Methylisoguanine			
a1m		^{g} 6.7 ^{aq} 0.0	^{g} 1×10^{-5} ^{aq} 1.00

a2m		^{g} 4.7 ^{aq} 3.5	^{g} 3×10^{-4} ^{aq} 0.003
a3m		^{g} 0.0 ^{aq} 3.8	^{g} 1.00 ^{aq} 0.002
a4m		^{g} 20.1 ^{aq} 9.6	^{g} 2×10^{-15} ^{aq} 9×10^{-8}

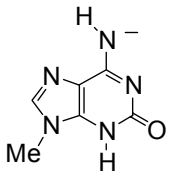
a5m		^{g} 22.4 ^{aq} 10.1	^{g} 4×10^{-17} ^{aq} 4×10^{-8}

Table S2. Neutral isoguanine in various media. Relative free energies (in kcal/mol) and populations (in parentheses) for tautomers of neutral isoguanine in media of varying dielectric constant (ε) are shown.[a] Structures are shown in Table S1. In bold faces are the tautomers having significant populations.

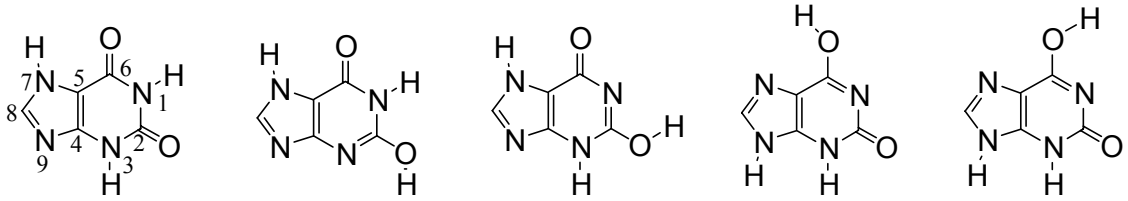
ε	**1**	**2**	**3**	**4**	**17**	**20**
1 (*g*)	5.5 (6×10^{-5})	4.9 (2×10^{-4})	**0.4 (0.34)**	**0.0 (0.66)**	19.0 (8×10^{-15})	6.8 (7×10^{-6})
2.2	1.5 (0.05)	1.3 (0.08)	**0.8 (0.18)**	**0.0 (0.68)**	12.2 (8×10^{-10})	2.8 (0.01)
4.7	**0.0 (0.49)**	**0.1 (0.43)**	2.6 (0.007)	1.7 (0.03)	7.2 (2×10^{-6})	1.4 (0.04)
8.9	**0.0 (0.55)**	**0.2 (0.39)**	4.1 (5×10^{-4})	4.6 (2×10^{-4})	4.9 (1×10^{-4})	1.3 (0.06)
38.9	**0.0 (0.52)**	**0.2 (0.39)**	6.4 (1×10^{-5})	6.4 (1×10^{-5})	2.7 (0.005)	1.0 (0.09)
80 (*aq*)	**0.0 (0.51)**	**0.2 (0.38)**	6.7 (6×10^{-6})	6.8 (5×10^{-6})	2.3 (0.01)	1.0 (0.10)

[a] The same probe radius as in water (1.40 Å) was used in all the calculations.

Xanthine

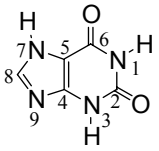
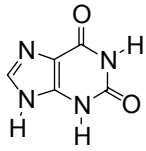
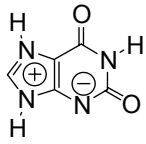
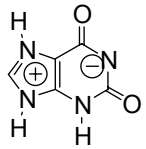
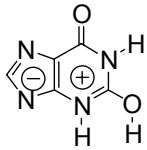
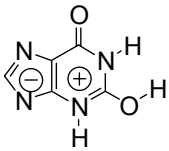
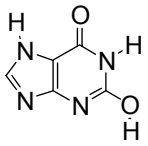
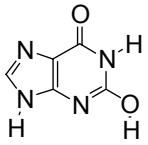
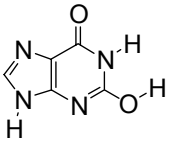
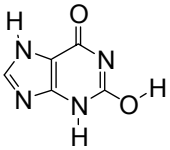
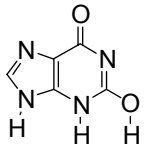
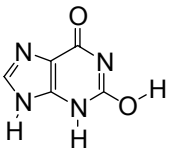
Naming convention for tautomers of xanthine

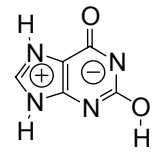
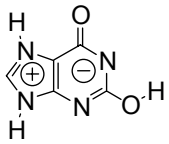
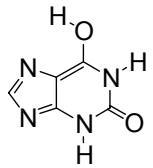
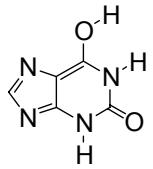
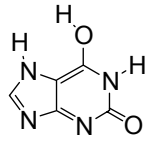
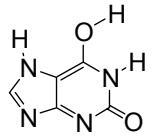
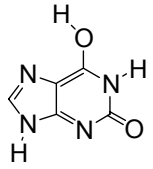
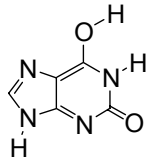
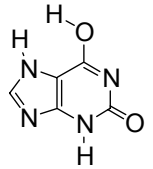
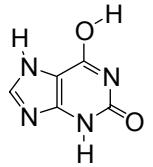
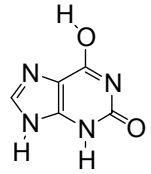
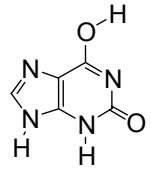
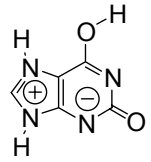
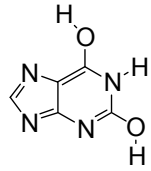
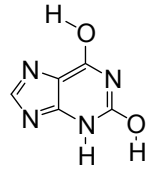
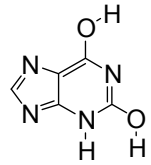
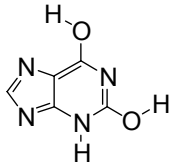
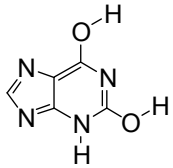
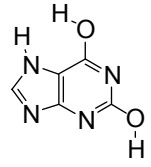
Numbers in each name denote the sites where acidic protons are attached. For enols, 2d (for "down") denotes O2H towards N3, 2u (for "up") for O2H towards N1, 6le (for "left") for O6H towards N7, and 6ri (for "right") for O6H towards N1. Several examples are shown below.

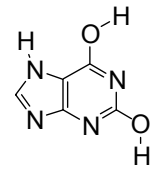
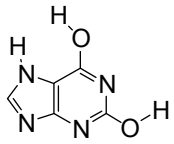
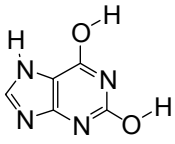
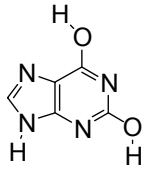
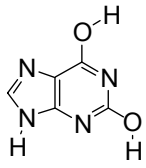
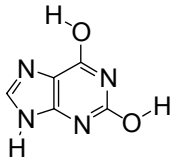
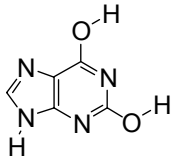
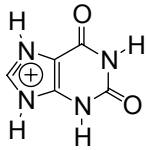
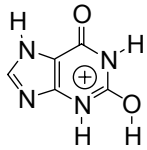
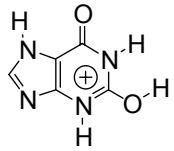
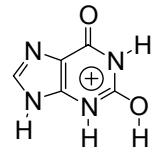
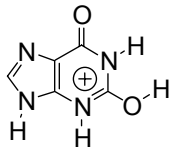
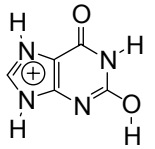
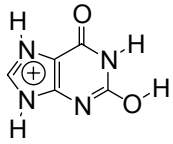
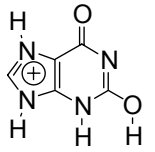
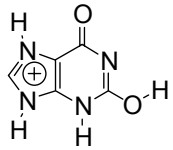
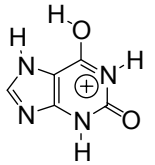
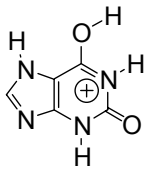
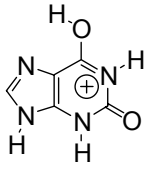
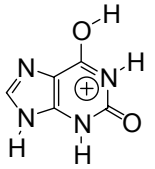


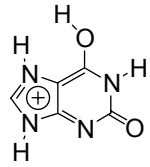
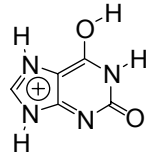
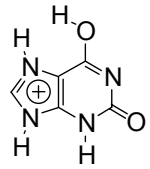
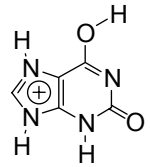
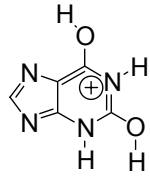
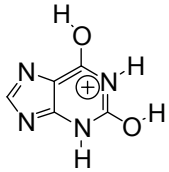
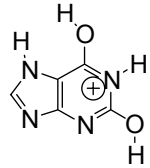
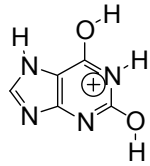
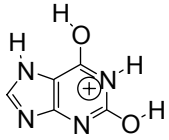
137 **12d7** **2u37** **36le9** **36ri9**

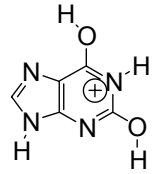
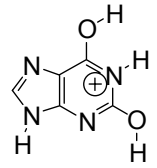
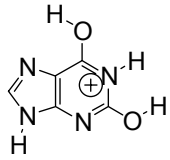
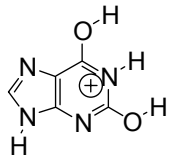
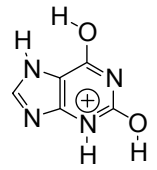
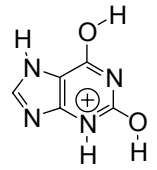
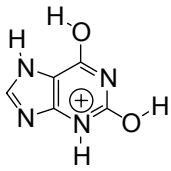
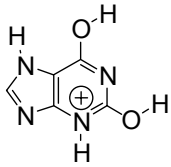
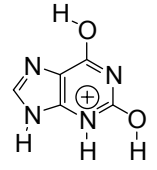
Table S3. Tautomers of xanthine. Relative free energies ($\Delta\Delta G$ in kcal/mol) and relative populations (f) are given in relation to the most stable tautomer of a particular group. Each group is labeled in boldface. Values for both the gas phase (g) and aqueous phase (aq) are indicated for each structure.

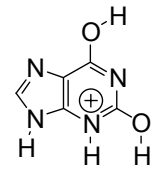
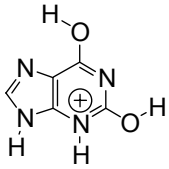
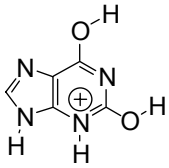
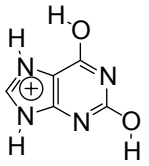
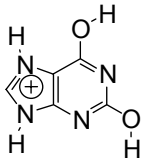
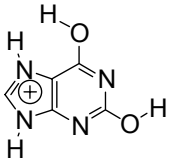
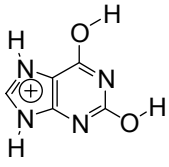
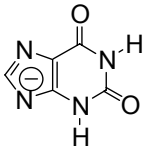
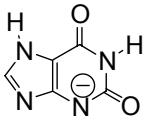
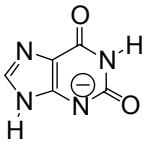
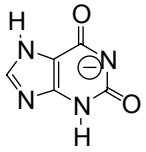
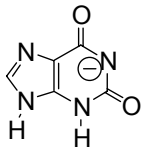
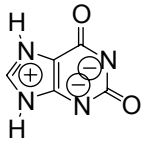
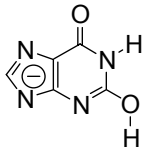
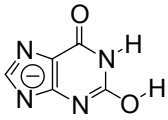
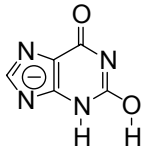
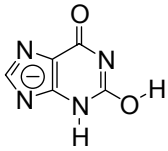
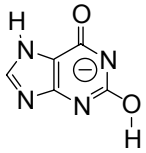
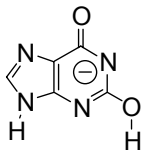
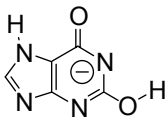
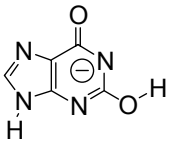
Name	Structure	$\Delta\Delta G$	f
Neutral Xanthine			
137		^{g} 0.0 ^{aq} 0.0	^{g} 1.0 ^{aq} 0.741
139		^{g} 9.1 ^{aq} 0.6	^{g} 2×10^{-7} ^{aq} 0.258
179		^{g} 23.2 ^{aq} 3.9	^{g} 9×10^{-18} ^{aq} 0.001
379		^{g} 45.5 ^{aq} 9.0	^{g} 4×10^{-34} ^{aq} 2×10^{-7}
12d3		^{g} 40.5 ^{aq} 20.7	^{g} 2×10^{-30} ^{aq} 4×10^{-16}
12u3		^{g} 39.9 ^{aq} 20.5	^{g} 5×10^{-30} ^{aq} 7×10^{-16}
12d7		^{g} 11.5 ^{aq} 10.4	^{g} 4×10^{-9} ^{aq} 2×10^{-8}
12d9		^{g} 13.0 ^{aq} 9.7	^{g} 3×10^{-10} ^{aq} 6×10^{-8}
12u9		^{g} 18.7 ^{aq} 10.9	^{g} 2×10^{-14} ^{aq} 7×10^{-9}
2u37		^{g} 17.1 ^{aq} 13.3	^{g} 3×10^{-13} ^{aq} 1×10^{-10}
2d39		^{g} 39.4 ^{aq} 16.7	^{g} 1×10^{-29} ^{aq} 4×10^{-13}
2u39		^{g} 29.2 ^{aq} 14.7	^{g} 4×10^{-22} ^{aq} 1×10^{-11}

2d79		^{g} 34.8 ^{aq} 13.6	^{g} 3×10^{-26} ^{aq} 8×10^{-11}
2u79		^{g} 32.5 ^{aq} 13.7	^{g} 2×10^{-24} ^{aq} 6×10^{-11}
136le		^{g} 19.0 ^{aq} 17.1	^{g} 1×10^{-14} ^{aq} 2×10^{-13}
136ri		^{g} 26.6 ^{aq} 16.9	^{g} 3×10^{-20} ^{aq} 3×10^{-13}
16le7		^{g} 34.0 ^{aq} 16.1	^{g} 1×10^{-25} ^{aq} 1×10^{-12}
16ri7		^{g} 33.0 ^{aq} 16.1	^{g} 6×10^{-25} ^{aq} 1×10^{-12}
16le9		^{g} 20.1 ^{aq} 14.4	^{g} 2×10^{-15} ^{aq} 2×10^{-11}
16ri9		^{g} 25.8 ^{aq} 14.6	^{g} 1×10^{-19} ^{aq} 2×10^{-11}
36le7		^{g} 25.6 ^{aq} 13.4	^{g} 2×10^{-19} ^{aq} 1×10^{-10}
36ri7		^{g} 16.1 ^{aq} 12.3	^{g} 2×10^{-12} ^{aq} 8×10^{-10}
36le9		^{g} 23.8 ^{aq} 13.9	^{g} 3×10^{-18} ^{aq} 5×10^{-11}
36ri9		^{g} 21.3 ^{aq} 12.7	^{g} 2×10^{-16} ^{aq} 4×10^{-10}
6ri79		^{g} 44.3 ^{aq} 17.4	^{g} 3×10^{-33} ^{aq} 1×10^{-13}
12d6le		^{g} 32.1 ^{aq} 27.6	^{g} 3×10^{-24} ^{aq} 4×10^{-21}
2d36le		^{g} 33.9 ^{aq} 26.5	^{g} 1×10^{-25} ^{aq} 3×10^{-20}
2d36ri		^{g} 34.7 ^{aq} 25.9	^{g} 4×10^{-26} ^{aq} 8×10^{-20}
2u36le		^{g} 26.1 ^{aq} 25.4	^{g} 8×10^{-20} ^{aq} 2×10^{-19}
2u36ri		^{g} 28.1 ^{aq} 24.5	^{g} 2×10^{-21} ^{aq} 7×10^{-19}
2d6le7		^{g} 26.2 ^{aq} 19.2	^{g} 6×10^{-20} ^{aq} 6×10^{-15}

2d6ri7		^{g} 18.0 ^{aq} 18.5	^{g} 6×10^{-14} ^{aq} 2×10^{-14}
2u6le7		^{g} 26.7 ^{aq} 19.5	^{g} 3×10^{-20} ^{aq} 4×10^{-15}
2u6ri7		^{g} 19.7 ^{aq} 18.5	^{g} 4×10^{-15} ^{aq} 2×10^{-14}
2d6le9		^{g} 17.8 ^{aq} 18.7	^{g} 8×10^{-14} ^{aq} 2×10^{-14}
2d6ri9		^{g} 16.2 ^{aq} 17.7	^{g} 1×10^{-12} ^{aq} 7×10^{-14}
2u6le9		^{g} 16.7 ^{aq} 18.8	^{g} 6×10^{-13} ^{aq} 1×10^{-14}
2u6ri9		^{g} 16.4 ^{aq} 17.6	^{g} 1×10^{-12} ^{aq} 8×10^{-14}
Protonated Xanthine			
1379		^{g} 3.5 ^{aq} 0.0	^{g} 0.003 ^{aq} 1.00
12d37		^{g} 9.6 ^{aq} 14.1	^{g} 8×10^{-8} ^{aq} 5×10^{-11}
12u37		^{g} 9.1 ^{aq} 13.9	^{g} 2×10^{-7} ^{aq} 7×10^{-11}
12d39		^{g} 22.5 ^{aq} 15.2	^{g} 3×10^{-17} ^{aq} 7×10^{-12}
12u39		^{g} 20.2 ^{aq} 15.3	^{g} 2×10^{-15} ^{aq} 6×10^{-12}
12d79		^{g} 0.0 ^{aq} 7.2	^{g} 0.967 ^{aq} 5×10^{-6}
12u79		^{g} 6.8 ^{aq} 9.1	^{g} 1×10^{-5} ^{aq} 2×10^{-7}
2d379		^{g} 28.6 ^{aq} 14.7	^{g} 1×10^{-21} ^{aq} 2×10^{-11}
2u379		^{g} 17.6 ^{aq} 13.0	^{g} 1×10^{-13} ^{aq} 3×10^{-10}
136le7		^{g} 8.8 ^{aq} 12.5	^{g} 3×10^{-7} ^{aq} 7×10^{-10}
136ri7		^{g} 7.8 ^{aq} 12.6	^{g} 2×10^{-6} ^{aq} 6×10^{-10}
136le9		^{g} 5.7 ^{aq} 12.5	^{g} 7×10^{-5} ^{aq} 7×10^{-10}
136ri9		^{g} 12.1 ^{aq} 13.0	^{g} 1×10^{-9} ^{aq} 3×10^{-10}

16le79		^{g} 23.3 ^{aq} 13.9	^{g} 8×10^{-18} ^{aq} 6×10^{-11}
16ri79		^{g} 19.8 ^{aq} 13.7	^{g} 3×10^{-15} ^{aq} 8×10^{-11}
36le79		^{g} 39.8 ^{aq} 13.9	^{g} 7×10^{-30} ^{aq} 6×10^{-11}
36ri79		^{g} 17.2 ^{aq} 12.1	^{g} 2×10^{-13} ^{aq} 1×10^{-9}
12d36le		^{g} 35.0 ^{aq} 32.7	^{g} 2×10^{-26} ^{aq} 9×10^{-25}
12u36le		^{g} 35.6 ^{aq} 32.6	^{g} 8×10^{-27} ^{aq} 1×10^{-24}
12d6le7		^{g} 14.9 ^{aq} 21.1	^{g} 1×10^{-11} ^{aq} 4×10^{-16}
12d6ri7		^{g} 15.1 ^{aq} 21.3	^{g} 8×10^{-12} ^{aq} 2×10^{-16}
12u6le7		^{g} 24.2 ^{aq} 22.9	^{g} 2×10^{-18} ^{aq} 1×10^{-17}

12d6le9		^{g} 5.1 ^{aq} 19.7	^{g} 2×10^{-4} ^{aq} 3×10^{-15}
12d6ri9		^{g} 14.2 ^{aq} 22.3	^{g} 4×10^{-11} ^{aq} 5×10^{-17}
12u6le9		^{g} 13.0 ^{aq} 21.5	^{g} 3×10^{-10} ^{aq} 2×10^{-16}
12u6ri9		^{g} 20.4 ^{aq} 21.3	^{g} 1×10^{-15} ^{aq} 2×10^{-16}
2d36le7		^{g} 18.0 ^{aq} 21.3	^{g} 6×10^{-14} ^{aq} 2×10^{-16}
2d36ri7		^{g} 9.1 ^{aq} 19.7	^{g} 2×10^{-7} ^{aq} 3×10^{-15}
2u36le7		^{g} 9.8 ^{aq} 19.8	^{g} 7×10^{-8} ^{aq} 3×10^{-15}
2u36ri7		^{g} 2.0 ^{aq} 18.1	^{g} 0.030 ^{aq} 5×10^{-14}
2d36le9		^{g} 19.8 ^{aq} 22.1	^{g} 3×10^{-15} ^{aq} 6×10^{-17}

2d36ri9		^{g} 18.4 ^{aq} 20.9	^{g} 3×10^{-14} ^{aq} 4×10^{-16}
2u36le9		^{g} 10.1 ^{aq} 20.5	^{g} 4×10^{-8} ^{aq} 9×10^{-16}
2u36ri9		^{g} 9.9 ^{aq} 19.3	^{g} 5×10^{-8} ^{aq} 7×10^{-15}
2d6le79		^{g} 17.4 ^{aq} 17.2	^{g} 2×10^{-13} ^{aq} 2×10^{-13}
2d6ri79		^{g} 6.2 ^{aq} 15.6	^{g} 3×10^{-5} ^{aq} 4×10^{-12}
2u6le79		^{g} 16.6 ^{aq} 17.9	^{g} 6×10^{-13} ^{aq} 8×10^{-14}
2u6ri79		^{g} 6.7 ^{aq} 15.8	^{g} 1×10^{-5} ^{aq} 3×10^{-12}
Deprotonated Xanthine			
13		^{g} 0.0 ^{aq} 1.1	^{g} 1.00 ^{aq} 0.12
17		^{g} 9.3 ^{aq} 1.2	^{g} 2×10^{-7} ^{aq} 0.097
19		^{g} 5.7 ^{aq} 0.0	^{g} 7×10^{-5} ^{aq} 0.78
37		^{g} 16.0 ^{aq} 3.2	^{g} 2×10^{-12} ^{aq} 0.003
39		^{g} 27.3 ^{aq} 4.3	^{g} 1×10^{-20} ^{aq} 5×10^{-4}
79		^{g} 52.6 ^{aq} 10.2	^{g} 3×10^{-39} ^{aq} 3×10^{-8}
12d		^{g} 18.0 ^{aq} 12.9	^{g} 7×10^{-14} ^{aq} 3×10^{-10}
12u		^{g} 25.4 ^{aq} 13.9	^{g} 2×10^{-19} ^{aq} 5×10^{-11}
2d3		^{g} 32.4 ^{aq} 16.9	^{g} 2×10^{-24} ^{aq} 3×10^{-13}
2u3		^{g} 23.6 ^{aq} 15.4	^{g} 5×10^{-18} ^{aq} 4×10^{-12}
2d7		^{g} 19.5 ^{aq} 11.0	^{g} 5×10^{-15} ^{aq} 7×10^{-9}
2d9		^{g} 22.8 ^{aq} 10.8	^{g} 2×10^{-17} ^{aq} 1×10^{-8}
2u7		^{g} 18.7 ^{aq} 11.1	^{g} 2×10^{-14} ^{aq} 6×10^{-9}
2u9		^{g} 20.6 ^{aq} 10.8	^{g} 7×10^{-16} ^{aq} 9×10^{-9}

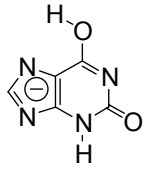
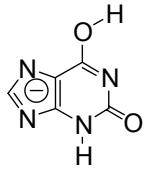
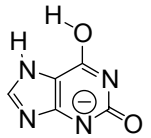
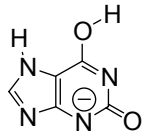
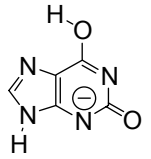
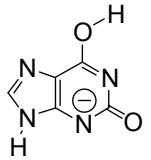
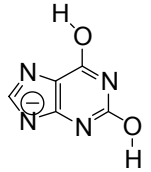
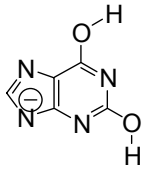
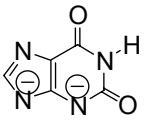
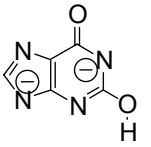
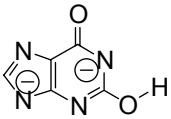
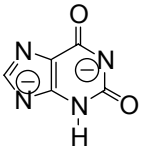
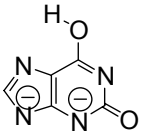
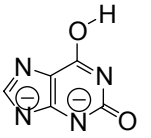
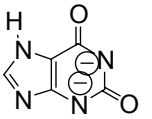
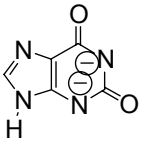
16le		^{g} 24.4 ^{aq} 16.9	^{g} 1×10^{-18} ^{aq} 3×10^{-13}
16ri		^{g} 31.8 ^{aq} 16.9	^{g} 5×10^{-24} ^{aq} 3×10^{-13}
36le		^{g} 13.5 ^{aq} 14.6	^{g} 1×10^{-10} ^{aq} 1×10^{-11}
36ri		^{g} 13.4 ^{aq} 13.1	^{g} 2×10^{-10} ^{aq} 2×10^{-10}
6le7		^{g} 42.0 ^{aq} 16.1	^{g} 2×10^{-31} ^{aq} 1×10^{-12}
6ri7		^{g} 32.5 ^{aq} 14.6	^{g} 1×10^{-24} ^{aq} 2×10^{-11}
6le9		^{g} 28.8 ^{aq} 14.5	^{g} 8×10^{-22} ^{aq} 2×10^{-11}
6ri9		^{g} 26.1 ^{aq} 13.6	^{g} 7×10^{-20} ^{aq} 9×10^{-11}
2d6le		^{g} 20.8 ^{aq} 21.4	^{g} 6×10^{-16} ^{aq} 2×10^{-16}
2d6ri		^{g} 21.7 ^{aq} 20.8	^{g} 1×10^{-16} ^{aq} 4×10^{-16}
Doubly Deprotonated Xanthine			
1		^{g} 0.0 ^{aq} 0.0	^{g} 1.00 ^{aq} 0.83
2d		^{g} 16.4 ^{aq} 11.0	^{g} 9×10^{-13} ^{aq} 7×10^{-9}
2u		^{g} 15.7 ^{aq} 10.8	^{g} 3×10^{-12} ^{aq} 9×10^{-9}
3		^{g} 4.6 ^{aq} 0.9	^{g} 4×10^{-4} ^{aq} 0.17
6le		^{g} 22.2 ^{aq} 14.1	^{g} 6×10^{-17} ^{aq} 3×10^{-11}
6ri		^{g} 21.8 ^{aq} 14.0	^{g} 1×10^{-16} ^{aq} 5×10^{-11}
7		^{g} 28.5 ^{aq} 4.8	^{g} 1×10^{-21} ^{aq} 3×10^{-4}
9		^{g} 27.0 ^{aq} 4.1	^{g} 2×10^{-20} ^{aq} 8×10^{-4}

Table S4. Gas-phase dipole moments (μ^g; in Debye) and solvation free energies ($\Delta\Delta G_{solv}$; in kcal/mol) for tautomers of neutral xanthine. Corresponding structures are given in Table S3.

	137	**139**	**179**	**379**	**12d3**	**12u3**	**12d7**	**12d9**
μ^g	4.51	7.58	11.00	15.41	10.38	9.96	0.59	6.62
$\Delta\Delta G_{solv}$	–28.53	–36.98	–47.90	–65.11	–48.31	–47.92	–29.62	–31.86
	12u9	**2u37**	**2d39**	**2u39**	**2d79**	**2u79**	**136le**	**136ri**
μ^g	4.38	3.59	11.87	9.86	11.97	9.80	2.59	4.35
$\Delta\Delta G_{solv}$	–36.32	–32.27	–51.20	–43.07	–49.80	–47.26	–30.45	–38.22
	16le7	**16ri7**	**16le9**	**16ri9**	**36le7**	**36ri7**	**36le9**	**36ri9**
μ^g	11.17	10.10	5.91	3.61	9.62	9.18	9.18	6.56
$\Delta\Delta G_{solv}$	–46.36	–45.46	–34.23	–39.80	–40.73	–38.47	–38.47	–37.20
	6ri79	**12d6le**	**2d36le**	**2d36ri**	**2u36le**	**2u36ri**	**2d6le7**	**2d6ri7**
μ^g	12.89	5.29	4.21	6.15	3.45	6.23	6.55	4.47
$\Delta\Delta G_{solv}$	–55.34	–33.02	–35.90	–37.35	–29.14	–32.08	–35.51	–27.99
	2u6le7	**2u6ri7**	**2d6le9**	**2d6ri9**	**2u6le9**	**2u6ri9**		
μ^g	7.49	6.34	5.86	3.85	3.56	0.96		
$\Delta\Delta G_{solv}$	–35.71	–29.74	–27.70	–29.96	–26.41	–27.23		

Table S5. Gas-phase dipole moments (μ^g; in Debye) and solvation free energies ($\Delta\Delta G_{solv}$; in kcal/mol) for tautomers of protonated xanthine. Corresponding structures are given in Table S3.

	1379	**12d37**	**12u37**	**12d39**	**12u39**	**12d79**	**12u79**	**2d379**
μ^g	10.72	4.33	3.18	11.31	9.16	7.07	4.73	13.24
$\Delta\Delta G_{solv}$	–92.48	–84.56	–84.27	–96.27	–93.84	–81.78	–86.62	–102.96
	2u379	**136le7**	**136ri7**	**136le9**	**136ri9**	**16le79**	**16ri79**	**36le79**
μ^g	10.54	7.61	6.02	4.32	1.74	12.57	9.97	14.42
$\Delta\Delta G_{solv}$	–93.60	–85.35	–84.21	–82.21	–88.12	–98.38	–95.11	–104.78
	36ri79	**12d36le**	**12u36le**	**12d6le7**	**12d6ri7**	**12u6le7**	**12d6le9**	**12d6ri9**
μ^g	11.53	6.75	7.68	5.77	5.92	8.32	1.48	3.29
$\Delta\Delta G_{solv}$	–94.04	–91.26	–92.01	–82.88	–82.85	–90.29	–74.35	–80.91
	12u6le9	**12u6ri9**	**2d36le7**	**2d36ri7**	**2u36le7**	**2u36ri7**	**2d36le9**	**2d36ri9**
μ^g	1.73	4.41	4.06	1.23	3.37	2.01	8.49	7.82
$\Delta\Delta G_{solv}$	–80.57	–88.10	–85.71	–78.37	–78.99	–72.93	–86.76	–86.44
	2u36le9	**2u36ri9**	**2d6le79**	**2d6ri79**	**2u6le79**	**2u6ri79**		
μ^g	5.48	5.27	10.93	8.01	9.79	6.98		
$\Delta\Delta G_{solv}$	–78.60	–79.58	–89.20	–79.66	–87.77	–79.89		

Table S6. Gas-phase dipole moments (μ^g; in Debye) and solvation free energies ($\Delta\Delta G_{solv}$; in kcal/mol) for tautomers of deprotonated xanthine. Corresponding structures are given in Table S3.

	13	**17**	**19**	**37**	**39**	**79**	**12d**	**12u**
μ^g	3.06	7.45	5.59	9.20	11.96	14.69	6.26	6.54
$\Delta\Delta G_{solv}$	–73.95	–83.08	–80.70	–87.77	–97.99	–117.44	–80.15	–86.63
	2d3	**2u3**	**2d7**	**2u7**	**2d9**	**2u9**	**16le**	**16ri**
μ^g	8.27	7.15	5.41	4.14	9.21	6.55	6.90	7.02
$\Delta\Delta G_{solv}$	–90.53	–83.25	–83.54	–82.66	–87.12	–84.84	–82.52	–89.87
	36le	**36ri**	**6le7**	**6ri7**	**6le9**	**6ri9**	**2d6le**	**2d6ri**
μ^g	3.04	0.67	12.19	10.80	9.37	6.70	0.91	3.39
$\Delta\Delta G_{solv}$	–73.89	–75.31	–100.96	–92.95	–89.28	–87.57	–74.44	–75.92

Table S7. Gas-phase dipole moments (μ^g; in Debye) and solvation free energies ($\Delta\Delta G_{solv}$; in kcal/mol) for tautomers of doubly deprotonated xanthine. Corresponding structures are given in Table S3.

	1	**2d**	**2u**	**3**	**6le**	**6ri**	**7**	**9**
μ^g	1.81	4.15	2.88	4.92	6.55	5.20	10.46	10.08
$\Delta\Delta G_{solv}$	–216.5	–221.9	–221.3	–220.2	–224.5	–224.3	–240.2	–239.3

Table S8. Microscopic (or site-specific) and macroscopic pK_a values of xanthine in water. Corresponding structures are given in Table S3.

	Protonated state	Deprotonated state	Microscopic pK_a	Macroscopic pK_a
(a) pK_{a1}	**1379** (100%)	**137** (74%)	0.06	–0.07
	1379 (100%)	**139** (26%)	0.51	
(b) pK_{a2}	**137** (74%)	**19** (78%)	6.91	6.93
	137 (74%)	**13** (12%)	7.72	
	137 (74%)	**17** (10%)	7.82	
	139 (26%)	**19** (78%)	6.45	
	139 (26%)	**13** (12%)	7.26	
	139 (26%)	**17** (10%)	7.36	
(c) pK_{a3}	**19** (78%)	**1** (83%)	11.54	11.57
	19 (78%)	**3** (17%)	12.23	
	13 (12%)	**1** (83%)	10.73	
	13 (12%)	**3** (17%)	12.43	
	17 (10%)	**1** (83%)	10.64	
	17 (10%)	**3** (17%)	11.33	

Table S9. Free energy costs (kcal/mol) of selected configurations of xanthine over the most stable configuration **137** under physiological conditions (aqueous solution at pH 7 and 298 K). Corresponding structures are given in Table S3.

Neutral	**139**	**179**	**379**	**12d9**	**12d7**	**36ri7**	**36ri9**	**2u37**	**16le9**	**2u6ri9**
$\Delta\Delta G^0_{aq,pH7}$[a]	0.6	3.9	9.0	9.7	10.4	12.3	12.7	13.3	14.4	17.6
$(\Delta\Delta G^0_g)$[a]	(9.1)	(23.2)	(45.5)	(13.0)	(11.5)	(16.1)	(21.3)	(17.1)	(20.1)	(16.4)
Anionic	**19**$^-$	**13**$^-$	**17**$^-$	**37**$^-$	**39**$^-$	**79**$^-$	**2u9**$^-$	**2u7**$^-$	**12d**$^-$	**6ri9**$^-$
$\Delta\Delta G^0_{aq,pH7}$[b]	–0.1	1.0	1.1	3.1	4.2	10.1	10.7	10.9	12.7	13.4
Doubly anionic	**1**$^{2-}$	**3**$^{2-}$	**7**$^{2-}$	**9**$^{2-}$	**2u**$^{2-}$	**6ri**$^{2-}$				
$\Delta\Delta G^0_{aq,pH7}$[c]	6.1	7.0	10.9	10.2	16.9	20.0				
Cationic	**1379**$^+$	**12d79**$^+$	**12u79**$^+$	**2u379**$^+$	**36ri79**$^+$	**136le7**$^+$	**136le9**$^+$			
$\Delta\Delta G^0_{aq,pH7}$[d]	9.5	16.7	18.1	22.5	21.6	22.0	21.9			

[a] $\Delta\Delta G^0(\mathbf{X}) = \Delta G^0(\mathbf{X}) - \Delta G^0(\mathbf{137})$ both in the gas phase and in aqueous phase,
[b] $\Delta\Delta G^0_{aq,pH7}(\mathbf{X}^-) = \Delta G^0_{aq}(\mathbf{X}^-) + [\Delta G^0_{aq}(H^+) + RT\ln 10^{-7}] - \Delta G^0_{aq}(\mathbf{137})$,
[c] $\Delta\Delta G^0_{aq,pH7}(\mathbf{X}^{2-}) = \Delta G^0_{aq}(\mathbf{X}^{2-}) + 2[\Delta G^0_{aq}(H^+) + RT\ln 10^{-7}] - \Delta G^0_{aq}(\mathbf{137})$,
[d] $\Delta\Delta G^0_{aq,pH7}(\mathbf{X}^+) = \Delta G^0_{aq}(\mathbf{X}^+) - [\Delta G^0_{aq}(H^+) + RT\ln 10^{-7}] - \Delta G^0_{aq}(\mathbf{137})$,
where $\Delta G^0_{aq}(H^+) + RT\ln 10^{-7} = -269.75 - 9.54 = -279.29$ (kcal/mol).

Table S10. Free energy costs (kcal/mol) of selected configurations of xanthine with a proton kept at N9 position over the most stable configuration **139** under physiological conditions (aqueous solution at pH 7 and 298 K). Corresponding structures are given in Table S3.

Neutral	**179**	**379**	**12d9**	**12u9**	**2u39**	**36ri9**	**16le9**	**16ri9**	**2u6ri9**
$\Delta\Delta G^0_{aq,pH7}$[a]	3.3	8.4	9.1	10.3	14.1	12.1	14.4	14.6	17.6
$(\Delta\Delta G^0_g)$[a]	(14.1)	(36.4)	(3.9)	(9.6)	(21.1)	(12.2)	(11.0)	(16.7)	(7.3)
Anionic	**19**$^-$	**39**$^-$	**79**$^-$	**2d9**$^-$	**2u9**$^-$	**6ri9**$^-$	**6le9**$^-$	**9**$^{2-}$	
$\Delta\Delta G^0_{aq,pH7}$[b,c]	–0.7	3.6	9.5	10.1	10.1	12.9	13.8	9.6	
Cationic	**1379**$^+$	**12d79**$^+$	**12u79**$^+$	**2u379**$^+$	**36ri79**$^+$	**136le9**$^+$			
$\Delta\Delta G^0_{aq,pH7}$[d]	8.9	16.1	18.0	21.9	21.0	21.3			

[a] $\Delta\Delta G^0(\mathbf{X}) = \Delta G^0(\mathbf{X}) - \Delta G^0(\mathbf{139})$ both in the gas phase and in aqueous phase,
[b] $\Delta\Delta G^0_{aq,pH7}(\mathbf{X}^-) = \Delta G^0_{aq}(\mathbf{X}^-) + [\Delta G^0_{aq}(H^+) + RT\ln 10^{-7}] - \Delta G^0_{aq}(\mathbf{139})$,
[c] $\Delta\Delta G^0_{aq,pH7}(\mathbf{X}^{2-}) = \Delta G^0_{aq}(\mathbf{X}^{2-}) + 2[\Delta G^0_{aq}(H^+) + RT\ln 10^{-7}] - \Delta G^0_{aq}(\mathbf{139})$,
[d] $\Delta\Delta G^0_{aq,pH7}(\mathbf{X}^+) = \Delta G^0_{aq}(\mathbf{X}^+) - [\Delta G^0_{aq}(H^+) + RT\ln 10^{-7}] - \Delta G^0_{aq}(\mathbf{139})$,
where $\Delta G^0_{aq}(H^+) + RT\ln 10^{-7} = -269.75 - 9.54 = -279.29$ (kcal/mol).